PCT/IN03/00393

THE PATENTS ACT, 1970

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.....

IN/03/393

.....In witness thereof

I have hereunto set my hand

Dated this the 19th day of December 2003
28th day of Agrahayana, 1925 (Saka)

(V.RENGASAMY)
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THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(Section 10)

18/12

"NOVEL TETRACYCLIC 3-SUSBTITUTED INDOLES HAVING SEROTONIN RECEPTOR AFFINITY USEFUL AS THERAPEUTIC AGENTS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

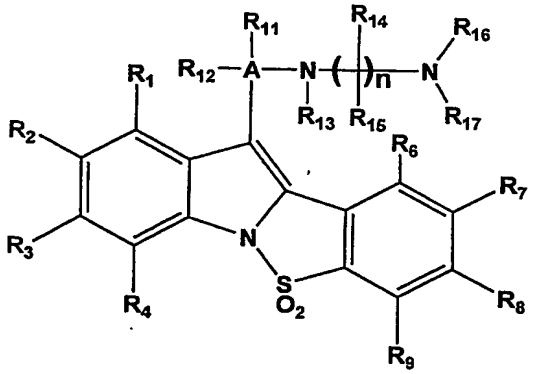
We, **SUVEN PHARMACEUTICALS LTD.**, an Indian company of Serene Chambers, Road No. 7, Banjara Hills, Hyderabad – 500 034, Andra Pradesh, India,

The following specification particularly describes the nature of the invention:

Novel tetracyclic 3-substituted indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them

Field of Invention:

The present invention relates to tetracyclic substituted 3-substituted indole compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutically acceptable compositions containing them and use of these compounds in medicine.



General Formula (I)

The present invention also relates to the process for preparing the compounds of general formula (I), their derivatives, their analogues, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, the novel intermediates involved therein and pharmaceutically acceptable compositions containing them.

The compounds of the general formula (I) of this invention are 5-HT ligands e.g. agonists or antagonists. Thus compounds of general formula (I) of this invention are useful for treating diseases wherein modulation of 5-HT activity is desired. Specifically, the compounds of this invention are useful in the treatment and / or prophylaxis of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders and sleep disorders. The compounds of general formula (I) of this invention are also useful

to treat psychotic, affective, vegetative and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs.

The compounds of general formula (I) of this invention are also useful to treat neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting. The compounds of general formula (I) of this invention are also useful in modulation of eating behavior and thus are useful in reducing the morbidity and mortality associated with excess weight.

Background of the Invention

Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic, and the serotenergic neurotransmitter systems. Serotonin has been implicated in a number of diseases and conditions, which originate in the central nervous system. These include diseases and conditions related to sleeping, eating, perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia and other bodily states. (References: Fuller, R.W., Drugs Acting on Serotonergic Neuronal Systems, Biology of Serotonergic Transmission, John Wiley & Sons Ltd., 1982, pp. 221-247; D. J. Boullin, Serotonin in Mental abnormalities, 1978, 1, 316; J. Barchas et. al., Serotonin and Behavior, 1973). Serotonin also plays an important role in the peripheral systems, such as the gastrointestinal system, where it has been found to mediate a variety of contractile, secretory and electrophysiologic effects.

Due to the broad distribution of serotonin within the body, there is lot of interest and use, in drugs that affect serotonergic systems. In particular, the receptor specific agonists and antagonists are of particular interest for the treatment of a wide range of disorders, including anxiety, depression, hypertension, migraine, obesity, compulsive disorders, schizophrenia, autism, neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting (References: M. D. Gershon et. al., The peripheral actions of 5-Hydroxytryptamine, 1989, 246; P. R. Saxena et. al., Journal of Cardiovascular Pharmacology, 1990, supplement 7, 15).

The major classes of serotonin receptors ($5\text{-}HT_{1\text{-}7}$) contain fourteen to eighteen separate receptors that have been formally classified (References: Glennon et al, Neuroscience and Behavioral Reviews, 1990, 14, 35 and D. Hoyer et al, Pharmacol. Rev., 1994, 46, 157-203). Recently discovered information regarding sub-type identity, distribution, structure and function suggests that it is possible to identify novel, sub-type specific agents having improved therapeutic profiles with lesser side effects. The $5\text{-}HT_6$

receptor was identified in 1993 (References: Monsma et al, Mol. Pharmacol., 1993, 43, 320-327 and M. Ruat et al, Biochem. Biophys. Res. Com., 1993, 193, 269-276). Several antidepressants and atypical antipsychotics bind to the 5-HT_6 receptor with high affinity and this binding may be a factor in their profile of activities (References: Roth et al, J. Pharm. Exp. Therapeut., 1994, 268, 1403-1410; Sleight et al, Exp. Opin. Ther. Patents, 1998, 8, 1217-1224; Bourson et al, Brit. J. Pharm., 1998, 125, 1562-1566; Boess et al, Mol. Pharmacol., 1998, 54, 577-583; Sleight et al, Brit. J. Pharmacol., 1998, 124, 556-562). In addition, 5-HT_6 receptor has been linked to generalized stress and anxiety states (Reference: Yoshioka et al, Life Sciences, 1998, 17/18, 1473-1477). Together these studies and observations suggest that compounds that antagonize the 5-HT_6 receptor will be useful in treating disorders of the central nervous system.

U.S. Pat. No. 4,839,377, and U.S. Pat. No. 4,855,314, refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent 2,035,310 refers to 3-aminoalkyl-1H-indole-5-thioamides and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Publication 303,506 refers to 3-polyhydro-pyridyl-5-substituted-1H-indoles. The compounds are said to have 5-HT_1 receptor agonists and vasoconstrictor activity and to be useful in treating migraine. European Patent Publication 354,777 refers to N-piperidinylindolylethyl-alkane sulfonamide derivatives. The compounds are said to have 5-HT_1 receptor agonists and vasoconstrictor activity and to be useful in treating cephalic pain.

European Patent Publication 438,230, refers to indole-substituted five-membered heteroaromatic compounds. The compounds are said to have "5-HT_1-like" receptor agonist activity and to be useful in the treatment of migraine and other disorders for which a selective agonist of these receptors is indicated.

European Patent Publication 313,397 refers to 5-heterocyclic indole derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

International Patent Publication WO 91/18897, refers to 5-heterocyclic indole

derivatives. The compounds are said to have exceptional properties for the treatment and prophylaxis of migraine, cluster headache, and headache associated with vascular disorders. These compounds are also said to have exceptional "5-HT_1-like" receptor agonism.

European Patent Publication 457,701 refers to aryloxy amine derivatives as having high affinity for 5-HT_{1D} serotonin receptors. These compounds are said to be useful for treating diseases related to serotonin receptor dysfunction, for example, migraine.

European Patent Publication 497,512 A2, refers to a class of imidazole, triazole and tetrazole derivatives which are selective agonists for "5-HT_1-like" receptors. These compounds are said to be useful for treating migraine and associated disorders.

International Patent Publication WO 93/00086, describes a series of tetrahydrocarbazole derivatives, as 5-HT_1 receptor agonists, useful for the treatment of migraine and related conditions.

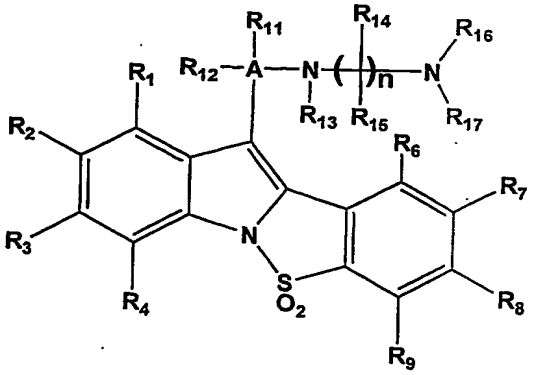
International Patent Publication WO 93/23396, refers to fused imidazole and triazole derivatives as 5-HT_1 receptor agonists, for the treatment of migraine and other disorders.

P. Schoeffter et al. refer to methyl 4-{4-[4-(1,1,3-trioxo-2H-1,2-benzoisothiazol-2-yl)butyl]-1-piperazinyl}1H-indole-3-carboxylate as a selective antagonist for the 5-HT_{1A} receptor in their paper "SDZ216-525, a selective and potent 5-HT_{1A} receptor antagonist" European Journal of Pharmacology, 244, 251-257 (1993).

International Patent Publication WO 94/06769, refers to 2-substituted-4-piperazine-benzothiophene derivatives that are serotonin 5-HT_{1A} and 5-HT_{1D} receptor agents useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

Summary of the Invention:

The present invention relates to novel tetracyclic substituted 3-substituted indole compounds of the general formula (I),



General Formula (I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates,

wherein A may be CH_2, C=O or SO_2; R_{11} and R_{12}, refer to substitutions whenever A is CH_2;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{11}, R_{12}, R_{14} and R_{15} may be same or different and represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, thio, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups selected from linear or branched $(C_1$-$C_{12})$alkyl, $(C_2$-$C_{12})$alkenyl, $(C_2$-$C_{12})$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1$-$C_{12})$alkoxy, cyclo$(C_3$-$C_7)$alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 or R_8 and R_9 together with carbon atoms to which they are attached may form a five or a six membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur" or "Selenium", and combinations of double bond and heteroatoms; or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a three to a six membered ring, optionally containing one or more double bonds and

optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur" or "Selenium", and combinations of double bond and heteroatoms;

R_{10}, may be same or different and represent hydrogen, halogeno, perhaloalkyl, trifluoromethylsulfonyloxy(OTf)aniline, substituted or unsubstituted groups selected from linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, $(C_1\text{-}C_{12})$alkoxy, cyclo$(C_3\text{-}C_7)$alkoxy, aryl, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyalkyloxy, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl arylalkyl, aralkoxyalkyl, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives;

R_{13}, R_{16} and R_{17} represents hydrogen, substituted or unsubstituted groups selected from linear or branched $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_3\text{-}C_7)$cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} along with either R_{16} or R_{17} and the two nitrogen atoms may form a 5 or 7–membered heterocyclic ring, which may be further substituted with R_{14} and R_{15}, and may have either one, two or three double bonds;

"n" is an integer ranging from 1 to 4, wherein the carbon chains which "n" represents may be either linear or branched.

Examples of such compound of general formula (I) are the following:

The compounds of general formula (I) of this invention are useful in the treatment and/ or prophylaxis of a condition wherein modulation of 5-HT activity is desired.

The present invention provides for use of the compounds of general formula (I) according to above, for the manufacture of the medicaments for use in the treatment and/ or prophylaxis of conditions such as, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders and sleep disorders; and can also include neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The compounds of general formula (I) of this invention can also be used to reduce psychotic, affective, vegetative and psychomotor symptoms of schizophrenia, the

extrapyramidal motor side effects of other antipsychotic drugs and also in chemotherapy-induced vomiting.

As compounds of general formula (I) as defined above are useful in modulation of eating behavior, these compounds can also be used to reduce morbidity and mortality associated with the excess weight.

The present invention provides a method for the treatment of a human or a animal subject suffering from a conditions such as, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders and sleep disorders; and can also include neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The present invention also provides a method for modulating 5-HT receptor function.

The present invention also includes a radiolabelled compound of general formula as a diagnostic tool for modulating 5-HT receptor function.

An effective amount of a compound of general formula I or its salt is used for producing medicaments of the present invention, along with conventional pharmaceutical auxiliaries, carriers and additives.

The present invention also relates to a pharmaceutical composition for treating and/or prophylaxis of disorders, a condition wherein modulation of 5-HT is desired in a mammal, preferably a human, comprising:

a. a pharmaceutically acceptable carrier
b. a compound of general formula (I) as defined above,
c. a 5-HT re-uptake inhibitor, preferably sertraline, or a pharmaceutically acceptable salt thereof;

wherein the amounts of each active compound (a compound of general formula I and a 5-HT re-uptake inhibitor), is such that the combination is effective in treating such a condition.

The present invention also relates to a method of treatment and/or prophylaxis of disorders, a condition wherein modulation of 5-HT is desired in a mammal, preferably a human, comprising:

a. a pharmaceutically acceptable carrier
b. a compound of general formula (I) as defined above,

c. a 5-HT re-uptake inhibitor, preferably sertraline, or a pharmaceutically acceptable salt thereof;

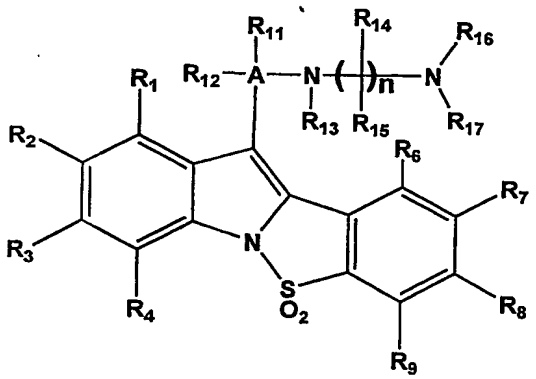
wherein the amounts of each active compound (a compound of general formula I and a 5-HT re-uptake inhibitor,) is such that the combination is effective in treating such a condition.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutical compositions containing them.

The present invention also relates to novel intermediates and their process of preparation, involved in the preparation of the compounds of general formula (I).

Detailed Description of the Invention:

The present invention relates to novel tetracyclic 3-substituted indole compounds of the general formula (I),



General Formula (I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates,

wherein A may be CH_2, C=O or SO_2; R_{11} and R_{12}, refer to substitutions whenever A is CH_2;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{11}, R_{12}, R_{14} and R_{15} may be same or different and represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, thio, amino, nitro, cyano,

formyl, amidino, guanidino, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 or R_8 and R_9 together with carbon atoms to which they are attached may form a five or a six membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur" or "Selenium", and combinations of double bond and heteroatoms; or R_{11} and R_{12} together with the carbon atom to which they are attached may form a three to a six membered ring, optionally containing one or more double bonds and optionally containing one or more heteroatoms selected from "Oxygen", "Nitrogen", "Sulfur" or "Selenium", and combinations of double bond and heteroatoms;

R_{10}, may be same or different and represent hydrogen, halogeno, perhaloalkyl, trifluoromethylsulfonyloxy(OTf)aniline, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyalkyloxy, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl arylalkyl, aralkoxyalkyl, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives;

R_{13}, R_{16} and R_{17} represents hydrogen, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} along with either R_{16} or R_{17} and the two nitrogen atoms may form a 5 or 7–membered heterocyclic ring, which may be further substituted with R_{14} and R_{15}, and may have either one, two or three double bonds;

"n" is an integer ranging from 1 to 4, wherein the carbon chains which "n" represents may be either linear or branched.

Suitable groups represented by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{11}, R_{12}, R_{14} and R_{15} wherever applicable may be selected from halogen atom such as fluorine, chlorine, bromine or iodine; perhaloalkyl particularly perhalo(C_1-C_6)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, fluoroethyl, difluoroethyl and the like; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_8)alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, iso-hexyl, heptyl, octyl and the like; substituted or unsubstituted (C_2-C_{12})alkenyl group such as ethylene, n-propylene pentenyl, hexenyl, heptynyl, heptadienyl and the like; (C_2-C_{12})alkynyl substituted or unsubstituted (C_2-C_{12})alkynyl group such as acetylene and the like; cyclo(C_3-C_7)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; cyclo(C_3-C_7)alkenyl group such as cyclopentenyl, cyclohexenyl, cycloheptynyl, cycloheptadienyl, cycloheptatrienyl and the like, the cycloalkenyl group may be substituted; (C_1-C_{12})alkoxy, especially, (C_1-C_6)alkoxy group such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, which may be substituted; cyclo(C_3-C_7) alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl group such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclo(C_1-C_6)alkyl, such as pyrrolidinylalkyl, piperidinylalkyl, morpholinylalkyl, thiomorpholinylalkyl, oxazolinylalkyl and the like, the heterocyclo(C_1-C_6)alkyl group may be substituted; heteroaralkyl group such as furanylmethyl, pyridinylmethyl, oxazolylmethyl, oxazolylethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclylalkyl moieties are as defined earlier and may be substituted; acyl groups such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acyloxy group such as CH_3COO, CH_3CH_2COO, C_6H_5COO and the like which may optionally be substituted, acylamino group such as CH_3CONH, CH_3CH_2CONH, C_3H_7CONH, C_6H_5CONH which may be

substituted, (C_1-C_6)monoalkylamino group such as CH_3NH, C_2H_5NH, C_3H_7NH, $C_6H_{13}NH$ and the like, which may be substituted, (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $CH_3(C_2H_5)N$ and the like, which may be substituted; arylamino group such as C_6H_5NH, $CH_3(C_6H_5)N$, $C_6H_4(CH_3)NH$, NH-C_6H_4-Hal and the like, which may be substituted; arylalkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; hydroxy(C_1-C_6)alkyl which may be substituted, amino(C_1-C_6)alkyl which may be substituted; mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl group which may be substituted, alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; aryloxyalkyl group such as $C_6H_5OCH_2$, $C_6H_5OCH_2CH_2$, naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$ and the like, which may be substituted; (C_1-C_6)alkylthio, thio(C_1-C_6)alkyl which may be substituted, alkoxycarbonylamino group such as C_2H_5OCONH, CH_3OCONH and the like which may be substituted; aryloxycarbonylamino group as C_6H_5OCONH, $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4CH_3OCONH$, $C_6H_4(OCH_3)OCONH$ and the like which may be substituted; aralkoxycarbonylamino group such $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2OCONH$, $C_6H_5CH_2OCON(CH_3)$, $C_6H_5CH_2OCON(C_2H_5)$, $C_6H_4CH_3CH_2OCONH$, $C_6H_4OCH_3CH_2OCONH$ and the like, which may be substituted; aminocarbonylamino group; (C_1-C_6)alkylaminocarbonylamino group, di(C_1-C_6)alkylaminocarbonylamino group; (C_1-C_6)alkylamidino group, (C_1-C_6)alkylguanidino, di(C_1-C_6)alkylguanidino groups, hydrazino and hydroxylamino groups; carboxylic acid or its derivatives such as amides, like $CONH_2$, alkylaminocarbonyl like CH_3NHCO, $(CH_3)_2NCO$, C_2H_5NHCO, $(C_2H_5)_2NCO$, arylaminocarbonyl like PhNHCO, NapthylNHCO and the like, aralkylaminocarbonyl such as $PhCH_2NHCO$, $PhCH_2CH_2NHCO$ and the like, heteroarylaminocarbonyl and heteroaralkylamino carbonyl groups where the heteroaryl groups are as defined earlier, heterocyclylaminocarbonyl where the heterocyclyl group is as defined earlier, carboxylic acid derivatives such as esters, wherein the ester moieties are alkoxycarbonyl groups such as unsubstituted or substituted phenoxycarbonyl, naphthyloxycarbonyl and the like; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group is as defined earlier, heterocycloxycarbonyl where heterocycle is as defined earlier and these carboxylic acid derivatives may be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, SO_2NHCF_3, $SO_2NHCO(C_1$-$C_6)$alkyl, SO_2NHCOaryl where the aryl group is as defined earlier and the sulfonic acid derivatives may be substituted; phosphoric acid and its derivatives as $P(O)(OH)_2$, $P(O)(OC_1$-C_6-alkyl$)_2$, $P(O)(O$-aryl$)_2$ and the like.

Suitable cyclic structures formed by the two adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 or R_8 and R_9 or R_{11} and R_{12} or R_{14}

and R_{15} together with the carbon atoms to which they are attached contain 5 to 6 ring atoms which may optionally contain one or more heteroatoms selected from oxygen, nitrogen or sulfur and optionally contain one or more double bonds and optionally contain combination of double bond and hetero atoms as described earlier. The cyclic structures may be optionally substiuted phenyl, naphthyl, pyridyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrimidinyl, pyrazinyl and the like. Suitable substituents on the cyclic structure formed by R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 or R_8 and R_9 or R_{11} and R_{12} together with the adjacent carbon atoms to which they are attached include oxo, hydroxy, halogen atom such as chlorine, bromine and iodine; nitro, cyano, amino, formyl, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, thioalkyl, alkylthio, phenyl or benzyl groups.

R_{13}, R_{16} and R_{17} preferably represents hydrogen, substituted or unsubstituted linear or branched $(C_1\text{-}C_{12})$alkyl like methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo$(C_3\text{-}C_7)$alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; $(C_3\text{-}C_7)$cycloheteroalkyl with heteratoms like "Oxygen", "Nitrogen", "Sulfur" or "Selenium" optionally containing one or two double or triple bonds. Suitable hetero cyclic rings formed between R_{13}, and either of R_{16} or R_{17} be selected from imidazolyl, pyrimidinyl, pyrazinyl, piperazinyl, diazolinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, imidazolyl, tetrazolyl and the like, the heteroaryl group may be substituted; heterocyclo$(C_1\text{-}C_6)$alkyl, such as pyrrolidinealkyl, piperidinealkyl, morpholinealkyl, thiomorpholinealkyl, oxazolinealkyl and the like, the heterocyclo$(C_1\text{-}C_6)$alkyl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclylalkyl moieties are as defined earlier and may be further substituted.

In the case of the compounds of general formula (I) having an asymmetric carbon atom the present invention relates to the D-form, the L-form and D,L- mixtures and in the case of a number of asymetric carbon atoms, the diastereomeric forms. Those compounds of general formula (I) which have an assymmetric carbon and as a rule are obtained as racemates can be separated into the optically active isomers in a manner known per se, for example using an optically active acid. However, it is also possible to employ an optically active compound from the start, a correspondingly optically active or diastereomeric compound then being obtained as the final compound.

In the case of the compounds of general formula (I) contain groups, which may exists in tautomeric forms, the present invention relates to all possible tautomeric forms and the possible mixture thereof.

In the case of the compounds of general formula (I) contain geometric isomerism the present invention relates to all of these geometric isomers.

Suitable pharmaceutically acceptable acid addition salts of compounds of the general formula (I) can be prepared of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, includes, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benezenesulfonate, p-tolunesulfonate, palmoate and oxalate. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to the above list.

Suitable pharmaceutically acceptable base addition salts of compounds of the general formula (I) can be prepared of the aforementioned acid compounds of this invention are those which form non-toxic base addition salts, includes, salts containing pharmaceutically acceptable cations, such as Lithium, sodium, potassium, calcium and magnesium, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, tromethamine and the like; ammonium or substituted ammonium salts.

In addition, pharmaceutically acceptable salts of the compound of formula (I) can be obtained by converting derivatives which have tertiary amino groups into the corresponding quarternary ammonium salts in the methods known in the literature by using quarternizing agents. Possible quarternizing agents are, for example, alkyl halides such as methyl iodide, ethyl bromide and n-propyl chloride, including arylalkyl halides such as benzyl chloride or 2-phenylethyl bromide.

In the description and the reaction scheme which follow R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, A and n are as defined previously for compound of general formula (I), and R is as defined elsewhere in the specification.

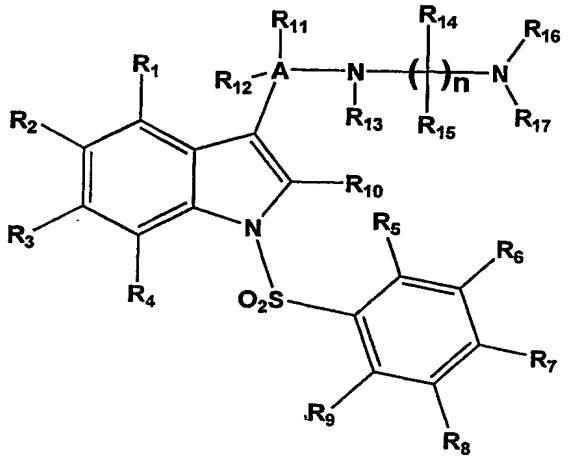
Compounds of general formula (I) can be prepared by any of the methods described below:

The present invention also provides processes for preparing compounds of general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and novel intermediates involved therein, which are as described below:

Preparation of Compounds of invention

Scheme I:

Compounds of general formula **(I)**, may be prepared by cyclizing a compound of formula **(II)** given below,



(II)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, A and n are as defined previously, or precursor thereof; and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula (I)

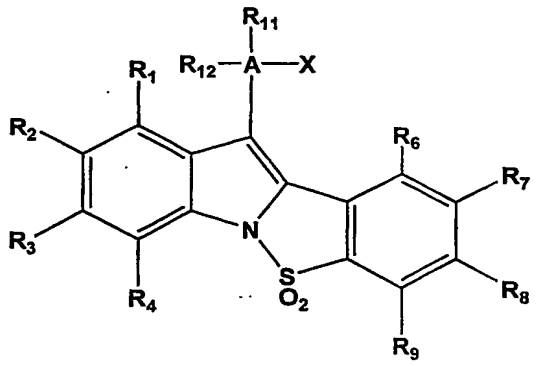
ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt or prodrug thereof.

Cyclization of compounds of formula **(II)** using tetrakis Palladium catalyst yields the compounds of this invention of general formula **(I)**. This cyclization reaction can be achieved using variety of triphenylphosphine palladium catalysts. The reaction may be affected in the presence of a base such as CH_3COOK. This reaction may be carried out in the presence of solvents such as THF, DMF, DMSO, DMA, DME, acetone and the like and preferably using Dimethylacetamide. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction temperature may range from 50 °C to 200 °C based on the choice of solvent and preferably at a temperature of 160 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 10 to 20 hours.

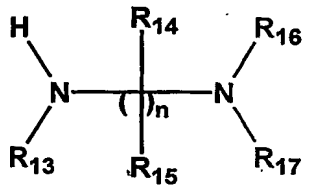
Scheme 2:

Compounds of general formula **(I)**, may be prepared by reacting a compound of formula **(III)** given below,



(III)

Where R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{11} and R_{12} are as defined in relation to formula **(I)**; X is a hydroxy or halogeno, for example a chloro, bromo or iodo; with a compound of formula **(IV)** or its acid addition salt,



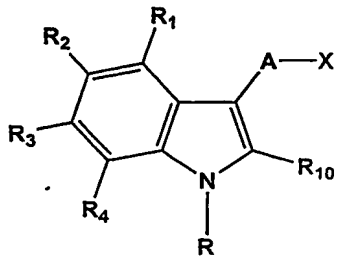
(IV)

where R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are as defined in relation to compound of formula **(I)** or precursor thereof; and thereafter if necessary:

Preparation of intermediates:

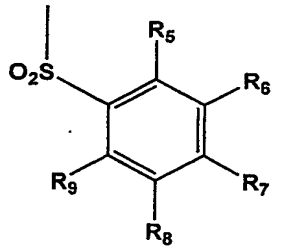
Route 1:

Compounds of general formula **(II)**, may be prepared by reacting a compound of formula **(V)** given below,

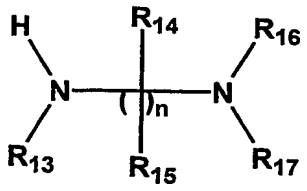


(V)

Where A, R_1, R_2, R_3, R_4, and R_{10} are as defined in relation to formula **(I)**, further R_{10} could be protected form thereof; R represents either of a suitable N-protecting group such as acetyl, triflouroacetyl, t-butoxycarbonyl, trityl, or a group such as,



where R_5, R_6, R_7, R_8 and R_9 are as defined earlier, X is a hydroxy or halogeno, for example a chloro, bromo or iodo; with a compound of formula **(IV)** or its acid addition salt,



(IV)

where R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are as defined in relation to compound of formula **(I)**.

Preferably the substituents selected for the compounds of formula (IV) and **(V)** are either inert to the reaction conditions or the sensitive groups are protected using suitable protecting groups. In case when R is a suitable protecting group, an additional step as described in **Route 2** is required to prepare compounds of formula **(V)**.

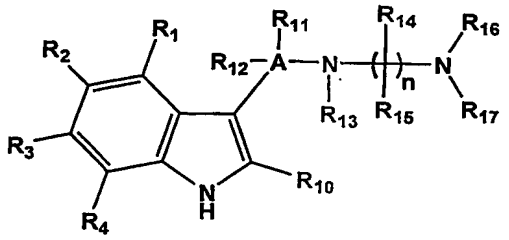
The above reaction is preferably carried out in a solvent such as THF, xylene, toluene, methanol, ethanol, propanol and the like and preferably using either acetone or DMF. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction mixture is generally heated to an elevated temperature or reflux temperature of the solvent, until the reaction is complete. A wide variety of acid-acceptor agents can be used in this condensation. However, preferred basic agents are sodium carbonate, sodium bicarbonate, potassium carbonate, sodium acetate, sodium alkoxides and the like, with a preferred basic agent being K_2CO_3. Reaction times of about 30 minutes to 72 hours are common. At the end of reaction, the volatile components are removed under reduced pressure. The reaction mixture can be optionally acidified before workup. The product can be isolated by precipitation, washed, dried and further purified by standard methods such as recrystallization, column chromatography etc.

Optional step (i) and (ii) can be carried out using conventional methods. These will depend upon the precise nature of the substituents on the indole in each case. Examples of suitable reactions are illustrated hereinafter.

Compounds of formula **(V)** may suitably be prepared by methods described in literature. Compounds of formula **(IV)** are commercially available, or they may be prepared by conventional methods or by modification, using known processes, of commercially available compounds of formula **(IV)**.

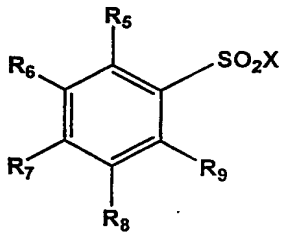
Route 2:

Alternatively, compounds of formula **(II)** may be prepared by reacting a compound of formula **(VI)** given below,



(VI)

where R_1, R_2, R_3, R_4, R_{10}, R_{11}, R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are as defined in relation to formula **(I)**, further R_{10} could be protected form thereof; with a compound of formula **(VII)**



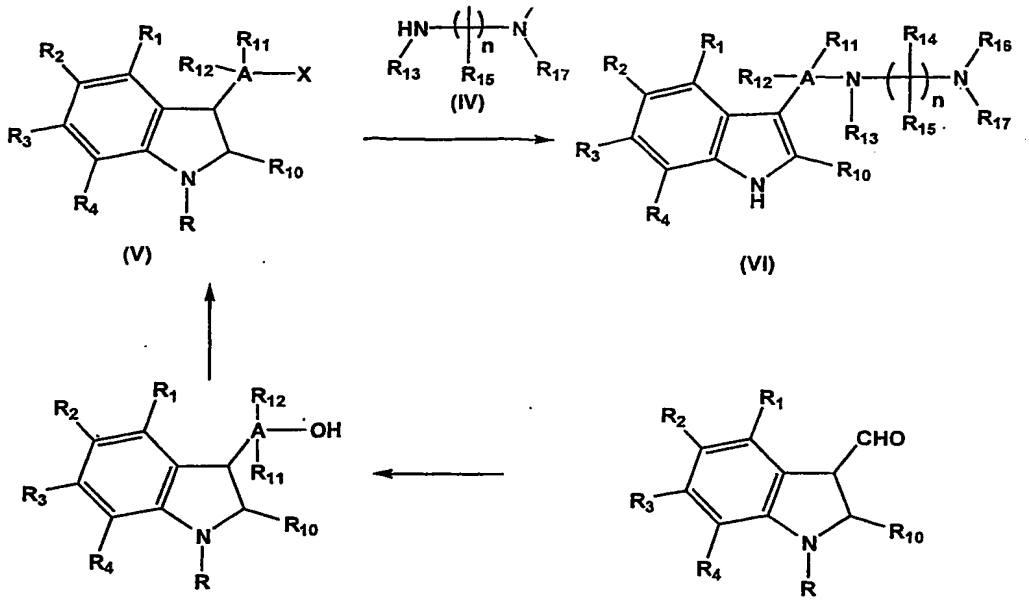
(VII)

where R_5, R_6, R_7, R_8 and R_9, are as defined in relation to formula **(I)** and X is a halogeno, preferably chloro or bromo; and thereafter if desired or necessary carrying out steps (i) and/or (ii) as described above.

Preferably the substituents selected for the compounds of formula **(VI)** and **(VII)** are either not affected by the reaction conditions or else the sensitive groups are protected using suitable groups.

Compounds of formula **(VI)** and **(VII)** are suitably reacted together in an inert organic solvent which includes, aromatic hydrocarbons such as toluene, o-, m-, p-xylene; halogenated hydrocarbons such as methylene chloride, chloroform, and chlorobenzene; ethers such as diethylether, diisopropyl ether, tert-butyl methyl ether, dioxane, anisole, and tetrahydrofuran; nitriles such as acetonitrile and propionitrile; ketones such as acetone, methyl ethyl ketone, diethyl ketone and tert-butyl methyl ketone; alcohols such as methanol, ethanol, n-propranol, n-butanol, tert-butanol and also DMF (N.N-dimethylformamide), DMSO (N.N-dimethyl sulfoxide) and water. The preferred list of solvents include DMSO, DMF, acetonitrile and THF. Mixtures of these in varying ratios can also be used. Suitable bases are, generally, inorganic compounds such as alkali metal hydroxides and alkaline earth metal hydroxides, such as lithium hydroxide, sodium hydroxide, potassium hydroxide and calcium hydroxide; alkali metal oxides and alkaline earth metal oxides, lithium oxide, sodium oxide, magnesium oxide and calcium oxide; alkali metal hydrides and alkaline earth metal hydrides such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal amides and alkaline earth metal amides such as lithium amide, sodium amide, potassium amide and calcium amide; alkali metal carbonates and alkaline earth metal carbonates such as lithium carbonate and calcium carbonate; and also alkali metal hydrogen carbonates and alkaline earth metal hydrogen carbonates such as sodium hydrogen carbonate; organometallic compounds, particularly alkali-metal alkyls such as methyl lithium, butyl lithium, phenyl lithium; alkyl magnesium halides such as methyl magnesium chloride, and alkali metal alkoxides and alkaline earth metal alkoxides such as sodium methoxide, sodium ethoxide, potassium ethoxide, potassium tert-butoxide and di-methoxymagnesium, further more organic bases e.g. triethylamine, triisopropylamine, and N-methylpiperidine, pyridine. Sodium hydroxide, Sodium methoxide, Sodium ethoxide, potassium hydroxide potassium carbonate and triethylamine are especially preferred. Suitably the reaction may be effected in the presence of phase transfer catalyst such as tetra-n-butylammonium hydrogensulphate and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. Reaction times may vary from 1 to 24 hrs, preferably from 2 to 6 hours, whereafter, if desired, the resulting compound is continued into a salt thereof.

Compounds of formula **(VI)** may be suitably prepared by methods analogous to those described above between the compound of formula **(IV)** and **(V)**, by the method analogous to that described in **Route 1**, wherein ring nitrogen is protected before the reaction.



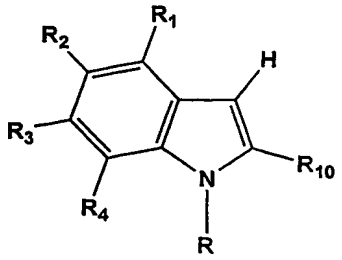
Flow Sheet 1

Compounds of formula **(VI)**, wherein R is particularly hydrogen can be prepared from other compounds of formula **(VI)**, wherein R is preferably an alkanoyl radical having 2-4 carbon atoms, wherein R_1, R_2, R_3, R_4, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, and R_{17} are as defined in relation to formula **(I)**, in a suitable solvent such as methanol or ethanol, with a basic agent, preferably an amine, ammonia or an alkali metal hydroxide, whereafter, if desired, the resulting compound is converted into a salt thereof. Conversion of hydroxyl groups to leaving groups is a conventional procedure for those of ordinary skill. The starting Indole-3-carboxaldehyde can be prepared by procedures known in art.

Compounds of formula **(VII)** are commercially available, or they may be prepared by conventional methods or by modification, using known processes, of commercially available compounds of formula **(VII)**.

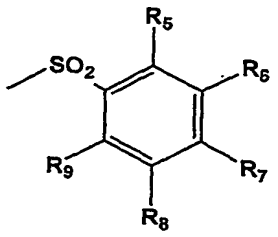
Route 3:

Alternatively, compounds of formula **(II)** may be prepared by reacting a compound of formula **(VIII)**

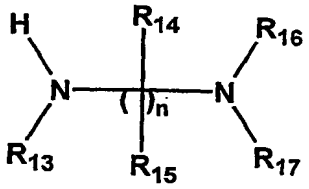


(VIII)

where R_1, R_2, R_3, R_4 and R_{10} are as defined in relation to formula (I), R_{10} could also be protected form thereof; R is defined as a suitable N-protecting group, such as acetyl, t-butoxycarbonyl, triflouroacetyl, or



where R_5, R_6, R_7, R_8 and R_9 are as defined earlier for compound of formula **(I)**, and with a compound of formula **(IV)** and formaldehyde,



(IV)

where R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are as defined in relation to compound of formula **(I)** or precursor thereof; and thereafter if desired or necessary carrying out steps (*i*) and/or (ii) above.

Preferably the substituents are either inert the reaction conditions or the sensitive groups are protected using suitable protecting groups. Whenever R is acetyl, an additional step described in **Route 2** is required to prepare compounds of general formula **(II)**.

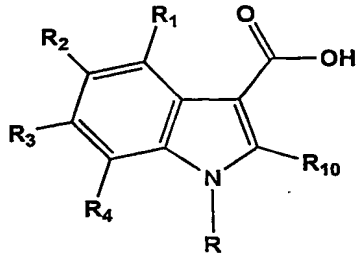
Compounds of formula **(IV)** are commercially available, or they may be prepared by conventional methods or by modification using known processes of commercially available compounds of formula **(IV)**.

The above reaction is preferably carried out at a temperature of 50 °C to 150 °C. the formaldehyde can be in the form of as aqueous solution i.e. 40 % formalin solution, or a polymeric form of formaldehyde such as paraformaldehyde or trioxymethylene. When such polymeric forms are used, a molar excess of mineral acid, for example hydrochloric acid, is added to regenerate the free aldehyde from the polymer. The reaction is preferably carried in an organic solvent inert to the conditions of the reaction, such as methanol, ethanol or 3-methylbutanol and the like or a mixture thereof, and preferably using either acetone or DMF. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction may be affected in the presence of a base such as K_2CO_3, Na_2CO_3, NaH or mixtures thereof. The reaction temperature may range from 20 °C to 150 °C based on the

choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

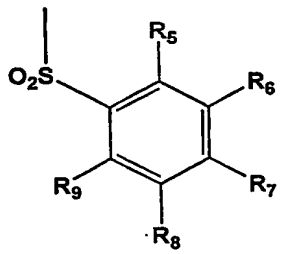
Route 4:

Compounds of general formula **(II)** may be prepared by reacting a compound of formula **(IX)** given below,

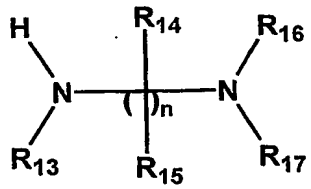


(IX)

Where R_1, R_2, R_3, R_4, and R_{10} are as defined in relation to formula **(I)**, further R_{10} could be protected form thereof; R represents either of a suitable N-protecting group such as acetyl, triflouroacetyl, t-butoxycarbonyl, or a group such as,



where R_5, R_6, R_7, R_8 and R_9 are as defined earlier, with a compound of formula **(IV)** or its acid addition salt,



(IV)

where R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are as defined in relation to compound of formula **(I)** or precursor thereof; by standard peptide coupling for example using bis(2-oxo-3-oxazolidinyl) phosphoric chloride (BOP-Cl) and carrying out reduction thereafter.

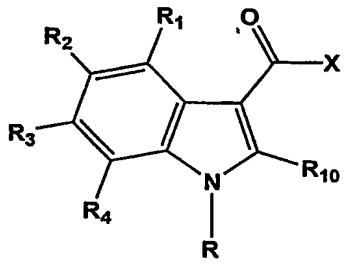
Alternetively, first N,N'-thionyl-diimidazole is prepared by reacting imidazole with thionyl chloride. The former is then reacted with the compound of formula **(IX)** N-(substituted indolyl)alkanoic acid and the resulting N-(substituted indolyl-alkanoyl)imidazole is reacted with 1-substituted piperazine compound of formula **(IV)**. If desired the N,N'-thionyl-diimidazole and N-(substituted indolyl- alkanoyl)imidazole intermediates can be isolated prior

to the next reaction in the succeeding step, but it is advantageous to carry out the entire sequence of steps upto formation of N-(substituted indolyl-alkanoyl)-4-substituted-piperazine in essentially one operation, that is by reacting each intermediate without isolation with the next succeeding reactant using the same solvent medium for the entire sequence of reactions. Suitable solvents are organic solvents inert under the conditions of the reactions, for excample tetrahydrofuran, diethylether, dibutyl ether and the like. The reactions are preferably conducted at a temperature in the range from about –10 °C to about 50 °C.

Amide intermediates can be reduced to the desired compound of formula (I), wherein A=CH_2, by the use of reducing agents capable of converting the amido functionality to an amino moiety. Such agents are, for example, lithium aluminum hydride or other complex aluminum hydrides. The reducing reactions are, performed in diethyl ether or tetrahydrofuran, or in a stable diborane complex such as boran-tetrahydrofuran or borane-dimethylsulphide or others (J. Org. Chem. 1982, 47, 1389) used in an appropriate solvent (e.g. tetrahydrofuran). Many other useful reducing agents are known to those skilled in the art (March, Advanced Organic Chemistry, Wiley Interscience Ed., 1992, 1212).

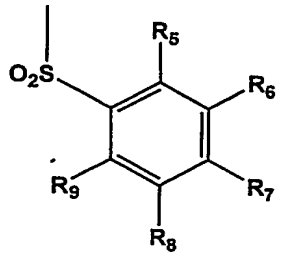
Route 5:

Compounds of general formula **(II)** may be prepared by reacting a compound of formula **(X)** given below,

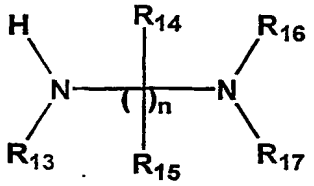


(X)

Where R_1, R_2, R_3, R_4, and R_{10} are as defined in relation to formula **(I)**, further R_{10} could be protected form thereof; X is a halogeno, for example a chloro, bromo or iodo; R represents either of a suitable N-protecting group such as acetyl, t-butoxycarbonyl, triflouroacetyl, or a group such as,



where R_5, R_6, R_7, R_8 and R_9 are as defined earlier, with a compound of formula **(IV)** or its acid addition salt,



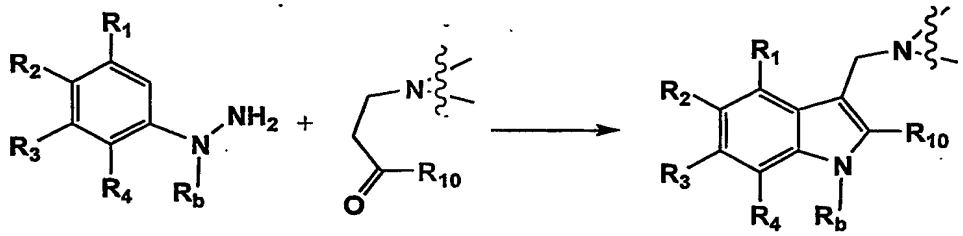
(IV)

where R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are as defined in relation to compound of formula **(I)** or precursor thereof.

The reaction is preferably carried out at a temperature in the range from about –5 °C to about 65 °C, in the presence of acid acceptor in an organic solvent inert under the conditions of the reactions, for example tetrahydrofuran, diethylether, ethylene chloride and the like. The purpose of acid acceptor is take up the hydrogen halide which is split out during the course of the reaction and includes sodium carbonate, sodium bicarbonate, potassium carbonate, sodium acetate, sodium alkoxides and the like. The acid acceptor can also be in the form of an excess quantity of 1-substituted piperazine.

Route 6:

Compounds of general formula **(II)** may be prepared by reacting a compound of formula **(XI)** given below, or its salt with the ketone amine compound of formula **(XII),**



(XI) **(XII)** **(III)**

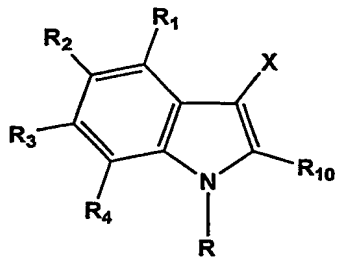
The process comprises of reacting the phenyl hydrazine compound of formula **(XI)** or its salt with the ketone amine compound of formula **(XII)** in presence of suitable solvent and an acid catalyst. The reaction may be carried out at temperature ranging between 60 °C to the reflux temperature of the solvent/s used, for about half-hour to 4 hours. Optionally, water formed in the reaction may be removed using the techniques known in the art. The reaction may be conducted in an inert atmosphere.

Suitable acid catalysts include mineral acids as well as organic acids, characterized in that glacial acetic acid, perchloric acid, trifluoroacetic acid, trichloroacetic acid, monochloroacetic acid, benzenesulfonic acid, hydrochloric acid, hydrobromic acid, sulfuric

acid, phosphoric acid, orthophosphoric acid, polyphosphoric acid and the like. Optionally Lewis acids such as aluminum chloride, titanium tetrachloride, zinc chloride etc. can be used as a catalyst in some cases. Suitable mechanism for removing water from a reaction mixture includes those described in the literature and known to a skilled artisan. Dehydrating agents such as sulfuric acid, molecular sieves, or removing water by azeotropic distillation are examples of techniques described in the prior art. Suitable solvents for the phenyl hydrazine of formula **(XI)** or its salt include ethers, alcohols, nitroalkanes, acetonitrile, dimethylsulfoxide, dimethyl formamide, and hexamethylphosphoramide. While suitable solvents for the ketone amine of formula **(XII)** includes inert solvents, such as, hydrocarbons, chlorinated hydrocarbons or acyclic ethers and the mixtures thereof.

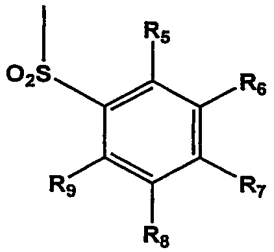
Route 7:

Compounds of general formula **(II)** wherein A is SO_2 may be prepared by converting a compound of formula **(XIII)** given below,



(XIII)

Where R_1, R_2, R_3, R_4, and R_{10} are as defined in relation to formula **(I)**, further R_{10} could be protected form thereof; X is a halogeno, for example a chloro, bromo or iodo; R represents either of a suitable N-protecting group such as acetyl, t-butoxycarbonyl, triflouroacetyl, or a group such as,



where R_5, R_6, R_7, R_8 and R_9 are as defined earlier, by metallation using, for example, t-buLi, followed by reaction with SO_2 gas and N-chlorosuccinimide. Thus giving compounds of general formula (V).

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be

achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, Ed J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The compounds of the present invention may contain one or more asymmetric centers and therefore they also exist as stereoisomers. The stereoisomers of the compounds of the present invention may be prepared by one or more ways presented below:

i) One or more of the reagents may be used in their optically active form.

ii) Optically pure catalyst or chiral ligands along with metal catalyst may be employed in the reduction process. The metal catalysts may be employed in the reduction process. The metal catalyst may be Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines (Principles of Asymmetric synthesis, J. E. Baldwin Ed., Tetrahedron series, 14, 311-316).

iii) The mixture of stereoisomers may be resolved by conventional methods such as forming a diastereomeric salts with chiral acids or chiral amines, or chiral amino alcohols, chiral amino acids. The resulting mixture of diastereomers may then be separated by methods such as fractional crystallization, chromatography and the like, which is followed by an additional step of isolating the optically active product by hydrolyzing the derivative (Jacques et. al., "Enantiomers, Racemates and Resolution", Wiley Interscience, 1981).

iv) The mixture of stereoisomers may be resolved by conventional methods such as microbial resolution, resolving the diastereomeric salts formed with chiral acids or chiral bases.

Chiral acids that can be employed may be tartaric acid, mandelic acid, lactic acid, camphorsulfonic acid, amino acids and the like. Chiral bases that can be employed may be cinchona alkaloids, brucine or a basic amino group such as lysine, arginine and the like.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium t-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, t-butanol, dioxane, isopropanol, isopropyl ether or mixtures thereof may be used. Organic bases such lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine,

tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, whereever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, salicyclic acid, citric acid, ascorbic acid, benzene sulfonic acid, p-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, malic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, DMF or a lower alkyl ketone such as acetone, or the mixtures thereof.

Different polymorphs may be prepared by crystallization of compounds of general formula (I) under different conditions such as different solvents or solvent mixtures in varying proportions for recrystallization, various ways of crystallization such as slow cooling, fast cooling or a very fast cooling or a gradual cooling during crystallization. Different polymorphs may also be obtained by heating the compound, melting the compound and solidification by gradual or fast cooling, heating or melting under vacuum or under inert atmosphere, and cooling under either vacuum or inert atmosphere. The various polymorphs may be identified by either one or more of the following techniques such as differential scanning calorimeter, powder X-ray diffraction, IR spectroscopy, solid probe NMR spectroscopy and thermal microsopy.

Another aspect of the present invention comprises of a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their derivatives, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides,their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers, auxiliaries and the like.

The pharmaceutical compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parental (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or a form suitable for administration by inhalation or insufflation.

The dose of the active compounds can vary depending on factors such as the route of administration, age and weight of patient, nature and severity of the disease to be treated and similar factors. Therefore, any reference herein to a pharmacologically effective amount of the compounds of general formula (I) refers to the aforementioned factors.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of an aerosol spray from a pressurized container or a nebulizer, or from a capsule using a inhaler or insufflator. In the case of a pressurized aerosol, a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas and the dosage unit may be determined by providing a valve to deliver a metered amount. The medicament for pressurized container or nebulizer may contain a solution or suspension of

hours), the product was isolated by distillation under reduced pressure. The residue was extracted with ethyl acetate (2 X 25 mL). The combined organic extracts were washed with water, followed by brine, dried over anhydrous sodium sulfate. The organic layer was evaporated under vacuum.

The residue could either be an oily liquid or solid mass was subjected to next reaction without further purification.

B. General procedure for the preparation of substituted 1-Benzenesulfonyl-3-chloromethyl-1H-indole, compounds of general formula (Vb).

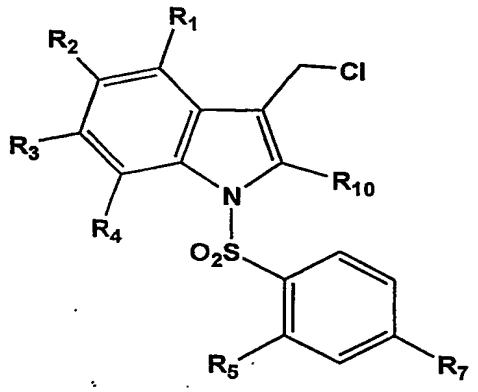
In a three necked round bottom flask equipped with pressure equalizing funnel, substituted (1-Benzenesulfonyl-1H-indol-3-yl)-methanol (0.01 mole) and dichloromethane (8 mL) were taken. Thionyl chloride (0.012 mole) was added slowly at room temperature and the reaction mixture was stirred well for one hour. After the completion of reaction, the product was isolated by distillation under reduced pressure. The residue was extracted with ethyl acetate (2 X 25 mL). The combined organic extracts were washed with water, followed by brine, dried over anhydrous sodium sulfate. The organic layer was evaporated under vacuum.

The residue could either be an oily liquid or solid mass. The oily mass was triturated with n-hexane to obtain a solid material.

Various derivatives of the compound represented by general formula (**Vb**) prepared according to either of above two routes are given below :

a) 1-(2-Bromobenzenesulfonyl)- 3-chloromethyl-1H-indole
b) 1-(2-Bromobenzenesulfonyl)-5-bromo-3- chloromethyl-1H-indole
c) 1-(2-Bromobenzenesulfonyl)-5-nitro-3- chloromethyl-1H-indole
d) 1-(2-Bromo-4-methoxybenzenesulfonyl)-5-bromo-3- chloromethyl-1H-indole

or their salts and solvates.



General formula (Vb series)

Comp. No. (Va) series	R_2	R_5	R_7	R_{10}
a)	H	Br	H	H
b)	Br	Br	H	H
c)	NO_2	Br	H	H
d)	Br	Br	OCH_3	H

C. General procedure for the preparation of substituted 1-Benzenesulfonyl-3-(4-methylpiperazin-1-ylmethyl)-1H-indole, compounds of general formula (Vb).

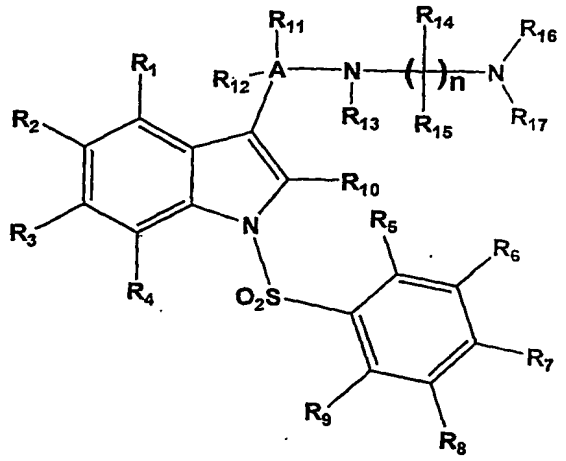
The substituted 1-Benzenesulfonyl-3-chloromethyl-1H-indole compounds, of general formula **(Vb)** were alkylated with 1-substituted piperazinyl **(IV)** compounds to obtain substituted 1-Benzenesulfonyl-3-(4-methylpiperazin-1-ylmethyl)-1H-indole, compound of general formula **(II)**.

Substituted 1-Benzenesulfonyl-3-chloromethyl-1H-indole (0.01 mole) was dissolved in **ethanol** (15 mL) and was transferred to three-necked flask. To this mixture triethylamine (0.015 moles) and N-methyl piperazine (0.01 mole) stirred at 25 °C and later for 3 hours. After the completion of reaction, the volatile substances were removed under reduced pressure. The residue was added ethyl acetate : water (1 : 1) mixture, followed by sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 X 20 mL). The combined organic extracts were washed with brine and the ethyl acetate was distilled of to obtain the crude intermediate.

Various derivatives of the compound represented by general formula **(II)** prepared according to the above procedure are given below :

1. 1-(4-Methylbenzenesulfonyl)-3-(4-methylpiperazin-1-ylmethyl)-1H-indole
2. 1-(4-Methylbenzenesulfonyl)-5-bromo-3-(4-methylpiperazin-1-ylmethyl)-1H-indole
3. 1-(4-Methylbenzenesulfonyl)-3-(4-methylpiperazin-1-ylmethyl)-5-nitro-1H-indole
4. 1-Benzenesulfonyl-5-bromo-3-(4-methylpiperazin-1-ylmethyl)-1H-indole

or their salts and solvates.



General formula (II)

Example No. (II) series	R_2	R_5	R_7	R_{10}	R_{16}
a)	H	Br	H	H	CH_3
b)	Br	Br	H	H	CH_3
c)	NO_2	Br	H	H	CH_3
d)	Br	Br	OCH_3	H	CH_3

The corresponding analytical data is given in Table 1.

Table – 1

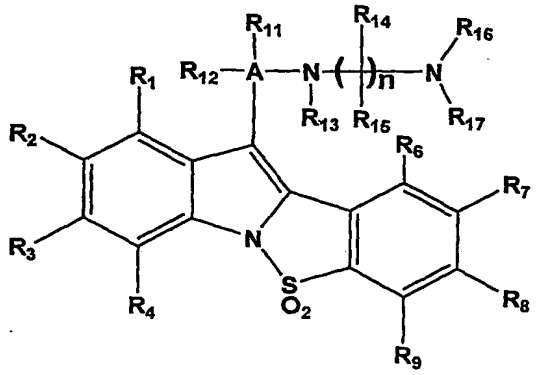
Example No. (II)series	Melting point (°C)	IR spectrum (KBr, Cm^{-1})	Mass Ion	NMR (δ ppm) (200MHz, $CDCl_3$)
a)	242 - 244. (HCl salt)	1573, 1447, 1373, 1179,	448	2.28 (s, 3H); 2.45 – 2.85 (m, 8H); 3.66 (s, 2H); 7.20 – 7.59 (m, 4H); 7.61 – 7.75 (m, 4H); 8.10 – 8.15 (dd, 1H).
b)	245-250 (HCl salt)	1573, 1446, 1373, 1317, 1179.		3.28 (s, 3H); 3.29-3.36 (m, 8H); 4.61(s, 2H);7.43-8.44 (m, 8H);
c)	228 – 248 (Dec.)	1527, 1448, 1381, 1356, 1178,		2.33, (s, 3H); 2.40 – 2.61 (m, 8H); 3.70 (s, 2H); 7.46 – 7.61 (m, 2H); 7.67 – 7.75 (m, 2H); 7.80 (s, 1H); 8.10 – 8.16 (dd, 1H); 8.28.–8.32 (dd, 1H); 8.68 – 8.70 (d, 1H).

d)	——	1585 1476, 1450 1363, 1309, 1175,		2.97 (s, 3H);3.34-3.86 (m, 8H); 4.86 (s, 2H); 7.29-8.43 (m, 8H);

D. General procedure for the preparation of cyclized compounds of general formula (I):

1-(2'-bromophenylsulfonyl)-substituted indole (0.286 moles) was taken in a 100 mL 3 necked round bottomed flask, along with N,N-dimethyl acetamide (40 mL), potassium acetate (0.286 moles, 0.281 g.) and dichloro bis(tri-o-tolylphosphine)palladium (0.0143 moles, 0.0126 g.). The reaction mixture was maintained under nitrogen atmosphere and was heated to 160 °C with stirring for 16 hrs. After the completion of reaction, excess of dimethyl acetamide was distilled off under reduced pressure and the residue was purified by silica gel column chromatography using 20 % methanol in ethyl acetate as an eluent. The final desired compound of general formula (I) can be further purified by preparation of their acid addition salts.

Various derivatives of the compound represented by general formula (I) prepared according to the above procedure are given below :



General formula (I)

Example No. (I) series	R_2	R_5	R_7	R_{10}	R_{16}
1.	H	Br	H	H	CH_3
2.	Br	Br	H	H	CH_3
3.	NO_2	Br	OCH_3	H	CH_3
4.	Br	Br	OCH_3	H	CH_3

The corresponding analytical data is given in Table 2.